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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,200	12/20/2001	Victor Knopov	INEX.P-008	9904

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EXAMINER	
RAZA, SAIRA B	

ART UNIT	PAPER NUMBER
1711	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,200	KNOPOV ET AL.	
	Examiner	Art Unit	
	Saira Raza	1711	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-49* is/are pending in the application.

4a) Of the above claim(s) *25-30 and 44-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 31-33, 37-40, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Semple (WO 98/51278) in view of Boller (EP 0 253 619 B1).

3. In reference to claims 31 and 43, Semple discloses a method of forming empty lipid vesicles, wherein the mixture of lipids and the buffered aqueous solution is combined and homogenized resulting in the formation of liposomes with a diameter between 100-500nm. Specifically, in reference to part (a) of claim 31, the lipid mixture (solution of ethanolic lipid) comprises 9.9mg/mL of lipid in an ethanol solution (100-95% by weight ethanol per weight of solvent). In reference to claim 31 part (c), the lipid mixture is combined with the buffered aqueous solution in a homogenizer, wherein the resulting lipid vesicles, prior to any extrusion step, are in a about 10% by weight ethanol per weight of lipid vesicle solution (Page : Lines :: 19:21-27, 26:12 to 27:11, 44:21, Example 1).

4. In reference to claims 32 and 33, Semple discloses the utilization of a citrate buffer with a pH less than 5 and a concentration range of 1-1000mM of anion, in the buffered aqueous solution. As exemplified in example 1, the buffer utilized was 300mM citrate buffer with a pH of 3.8.

5. In reference to claims 37 and 38, Semple discloses that the lipid mixture (ethanolic lipid) comprises a PEG-lipid conjugate, cationic lipid, and a neutral lipid. Specifically, the lipid portion of the ethanolic lipid comprises a PEG-lipid conjugate, cationic lipid, neutral lipid, and cholesterol in a ratio by weight of about 5:25:25:45 (14:6 to 20:7).

6. In reference to claims 39 and 40, the concentration of the lipid in the ethanolic lipid is less than 50mM, additionally, the concentration of lipid in the ethanolic lipid is less than about 25mg/mL (19:28 to 20:7, Example 1).

7. Semple fails to teach: a) the injection of the ethanolic lipid into the aqueous buffer through an injection port of diameter 2 mm or less and b) homogenizing by turbulent passage though a static mixer. Hence attention is directed towards the Boller reference.

8. Boller teaches a method for the preparation of small unilammellar vesicles via the ethanol injection technique. The liposomes are formed by injecting an ethanolic solution of phospholipids into an aqueous component consisting of a buffer and then mixing under high speeds. Specifically, Boller teaches that the ethanolic solution of lipids is injected into the aqueous buffer solution through one or more nozzles, wherein the nozzle diameter is 0.1 to 20 mm. Boller also discloses that the homogenization should be completed in a suitable vessel (like static mixer) which can be adapted to effect homogenization by effecting great turbulence during mixing of the lipid solution into the aqueous buffer. Boller discloses that the ethanol injection technique utilizing the nozzles and homogenization with turbulence is preferred because no further treatment of the liposomes such as ultrasonification, filtration, centrifugation or dialysis, is required prior to use and this process can be used for encapsulating active materials on a large scale (Page 3, Lines 9-12, 23-27, 33-35, 42-51; page 4, lines 22-37, examples 1-4). Wherein the claimed nozzle diameter of about 2 mm or less overlaps or lies inside the range disclosed by the prior art, a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

9. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized an ethanol injection technique wherein the nozzle diameter is between 0.1

to 20mm, and to have subsequently homogenized the lipid solution with the aqueous buffer in a static mixer with turbulence in the vesicle formation process of Semple in view of the teachings of Boller order to avoid further treatment of the liposomes and to utilize a process with capabilities to encapsulate active materials on a large scale.

10. Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Semple and Boller as applied to claim 31 above, and further in view of Webb et al. (US Patent No. 5,543,152).

11. The disclosures of Semple and Boller are provided above. The combined disclosure fails to teach an ethanolic lipid, which comprises sphingomyelin, cholesterol, or sphingomyelin and cholesterol in a ratio by weight of from 1:4 to about 4:1. Hence attention is directed towards the Webb reference.

12. Webb discloses a liposome have a membrane composed of sphingomyelin and cholesterol, wherein the weight ratio of sphingomyelin to cholesterol falls in the range of 1:4 to about 4:1. Furthermore, he discloses that liposomal formulations based on sphingomyelin and cholesterol have several advantages when compared to other formulations, specifically, the sphingomyelin/cholesterol combination produces liposomes which are much more stable to acid hydrolysis, have significantly better drug retention characteristics, have better loading characteristics into tumors and the like, and show significantly better anti-tumor efficacy than other liposomal formulations which were tested (2:23-34, 4:25-33).

13. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized a lipid comprising sphingomyelin, cholesterol, or sphingomyelin and cholesterol in a ratio by weight of from 1:4 to about 4:1 in the vesicle formation process of Semple in view of the teachings of Webb in order to produces liposomes which are much more stable to

acid hydrolysis, have significantly better drug retention characteristics, and have better loading characteristics into tumors and the like.

14. Claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Semple and Boller as applied to claim 31 above, and further in view of Gass (US Patent No. 5,317,043).

15. The disclosures of Semple and Boller are provided above. Boller discloses that homogenization should be completed in a suitable vessel (like static mixer) which can be adapted to effect homogenization by effecting great turbulence during mixing of the lipid solution into the aqueous buffer. However, the combination of references does not teach mixing at speeds where the Reynolds Number for the turbulence is greater than 2000, specifically greater than 3000. Hence attention is directed towards the Gass reference.

16. Gass discloses a process where rapid, intermittent mixing of solutions in a static mixer with turbulent flow results in the formation of particles. The Reynolds number of the turbulence is above 2000. The advantage of using this type of mixing is the minimal time requirement, only 0.1-2 seconds. Additionally, by rapidly converting the turbulent flow into a preferably laminar ripening flow, it is ensured that there is no increase in the size of the particles through their growing together (1:46 to 2:16). Wherein the claimed Reynolds number of greater than 2000 and greater then 3000 overlaps or lies inside the range disclosed by the prior art, a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

17. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to homogenize the lipid vesicles (ethanolic lipid solution and aqueous buffer) via turbulent passage in a static mixer where the Reynolds Number of the turbulence is greater than 2000 or 3000

in the vesicle formation process of Semple and Boller in view of the teachings of Gass in order to utilize minimal time for mixing and allow for other processing techniques which minimize agglomeration.

Response to Arguments

18. Applicant's arguments with respect to claims 31-43 have been considered but are moot in view of the new ground(s) of rejection.

19. Applicant should note that the WO 98/51278 reference is prior art under 35 U.S.C. 102(a) and cannot be overcome by a statement of common ownership.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Saira Raza whose telephone number is (571) 272-3553. The examiner can normally be reached on Monday-Friday from 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Seidleck can be reached on (571) 272-1078. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

IRINA ZEMEL
PRIMARY EXAMINER